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PTO/SB/05 (08-00)

Approved for use through 10/31/2002. OMB 0651-0032

Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. B00-001-3

First Named Inventor or Application Identifier Ames et al.

Title Primary N-hydroxylamines

Express Mail Label No. EV324953194US

EV324953194US

ADDRESS TO: Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. X *Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)
2. X Applicant claims small entity status (see 37 CFR 1.27)
3. X Specification (Total Pages 59)
(preferred arrangement set forth below)
 - Descriptive Title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to sequence listing, a table, or a computer program listing appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claims
 - Abstract of the Disclosure
4. Drawings(s) (35 USC 113) (Total Sheets)
5. X Oath or Declaration (Total Pages 1)
 - a. Newly Executed (Original or Copy)
 - b. X Copy from a Prior Application (37 CFR 1.63(d))
(for Continuation/Divisional with Box 17 completed)
 - i. DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. Application Data Sheet. See 37 CFR 1.76
7. CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix)

22388 U.S. PTO
10/713432



8. Nucleotide and/or Amino Acid Sequence Submission

(if applicable, all necessary)

- a. ☐ Computer Readable Form (CRF)
b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ paper
c. ☐ Statement verifying identity of above copies
d. ☐ Request to use CRF from another application

ACCOMPANYING APPLICATION PARTS

9. ☒ Assignment Papers (cover sheet & documents(s))
10. ☒ 37 CFR 3.73(b) Statement (where there is an assignee)
☒ Power of Attorney
11. ☐ English Translation Document (if applicable)
12. ☒ a. Information Disclosure Statement (IDS)/PTO-1449
☐ b. Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. ☒ Other: Transmittal letter and Remington ref. (3p)

17. Priority

This application claims priority to prior application No: 10/038,135, filed 10/20/01, having the same title and inventors

Prior application information: Examiner Jones, D. Group Art Unit 1614

The entire disclosure of the prior application, from which an oath or declaration is supplied under 5b, is considered a part of the disclosure of the accompanying application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

18. Correspondence Address

☒ Customer Number or Bar Code Label 23379
(Insert Customer No. or Attach Bar Code Label here)

or

☒ Correspondence Address Below

NAME Richard Aron Osman

SCIENCE & TECHNOLOGY LAW GROUP

ADDRESS 75 Denise Drive

CITY Hillsborough STATE California ZIP CODE 94010

Country U.S.A. TELEPHONE (650) 343-4341 FAX (650) 343-4342

Name: Richard Aron Osman Registration No: 36,627

Signature:  Date: November 13, 2003

16569 U.S. PTO
11303

FEE TRANSMITTAL EFFECTIVE OCTOBER 1, 2003

Fees are subject to annual revision

TOTAL AMOUNT OF PAYMENT (\$) \$758.00

Complete if Known:

Application No. Not yet assigned
 Filing Date Herewith
 First Named Inventor Ames et al.
 Group Art Unit Not yet assigned
 Examiner Name Not yet assigned
 Attorney Docket No. B00-001-3

METHOD OF PAYMENT (check one)

1. ☒ The Commissioner is hereby authorized to charge indicated fees to:
- ☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17 and credit any over payments to:
- ☒ Applicant claims small entity status. See 37 CFR 1.27
- Deposit Account Number 19-0750
 Deposit Account Name Science & Technology Law Group
2. ☒ Payment Enclosed
☒ Check
☐ Money Order
☐ Other

FEE CALCULATION

1. BASIC FILING FEE

| Large Entity | | Small Entity | | Fee Description | Fee Paid |
|--------------|----------|--------------|----------|------------------------------------|-------------------|
| Fee Code | Fee (\$) | Fee Code | Fee (\$) | | |
| 1001 | 770 | 2001 | 385 | Utility application filing fee | <u>385.</u> |
| 1002 | 340 | 2002 | 175 | Design application filing fee | <u> </u> |
| 1003 | 530 | 2003 | 265 | Plant filing fee | <u> </u> |
| 1004 | 770 | 2004 | 385 | Reissue filing fee | <u> </u> |
| 1005 | 160 | 2005 | 80 | Provisional application filing fee | <u> </u> |
| SUBTOTAL (1) | | | | | <u>\$ 385.00</u> |

2. CLAIMS

| | | | Extra | | Fee from below | | Fee Paid |
|---------------------------|-----------|--------------|-----------|---|-------------------|---|------------------|
| Total Claims | <u>57</u> | - 20 = | <u>37</u> | X | <u>9.00</u> | = | <u>333.00</u> |
| Independent Claims | <u>1</u> | - 3 = | <u>0</u> | X | <u> </u> | = | <u>0</u> |
| Multiple Dependent Claims | | | <u>0</u> | X | <u> </u> | = | <u>0</u> |
| Large Entity | | Small Entity | | Fee Description | | | Fee Paid |
| Fee Code | Fee (\$) | Fee Code | Fee (\$) | | | | |
| 1202 | 18 | 2202 | 9 | Claims in excess of twenty | | | <u>333.00</u> |
| 1201 | 86 | 2201 | 43 | Independent claims in excess of 3 | | | <u>0</u> |
| 1203 | 290 | 2203 | 145 | Multiple dependent claim | | | <u>0</u> |
| 1204 | 86 | 2204 | 43 | Reissue independent claims over original patent | | | <u>0</u> |
| 1205 | 18 | 2205 | 9 | Reissue claims in excess of 20 and over original patent | | | <u>0</u> |
| SUBTOTAL (2) | | | | | | | <u>\$ 333.00</u> |

FEE CALCULATION (continued)

3. ADDITIONAL FEES

| <u>Large Entity</u> | | <u>Small Entity</u> | | <u>F</u> | <u>Description</u> | <u>Fee Paid</u> |
|---------------------------|-------------|---------------------|-------------|----------|--|-----------------|
| <u>Fee</u> | <u>Fee</u> | <u>F e</u> | <u>Fee</u> | | | |
| <u>Cod</u> | <u>(\$)</u> | <u>Code</u> | <u>(\$)</u> | | | |
| 1051 | 130 | 2051 | 65 | | Surcharge - late filing fee or oath | |
| 1052 | 50 | 2052 | 25 | | Surcharge - late provisional filing fee or cover sheet | |
| 1053 | 130 | 1053 | 130 | | Non-English specification | |
| 1812 | 2,520 | 1812 | 2,520 | | For filing a request for ex parte reexamination | |
| 1804 | 920* | 1804 | 920* | | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | | Extension for response within first month | |
| 1252 | 420 | 2252 | 210 | | Extension for response within second month | |
| 1253 | 950 | 2253 | 475 | | Extension for response within third month | |
| 1254 | 1,480 | 2254 | 740 | | Extension for response within fourth month | |
| 1255 | 2,010 | 2255 | 1,005 | | Extension for response within fifth month | |
| 1401 | 330 | 2401 | 165 | | Notice of Appeal | |
| 1402 | 330 | 2402 | 165 | | Filing a brief in support of an appeal | |
| 1403 | 290 | 2403 | 145 | | Request for oral hearing | |
| 1451 | 1,510 | 1451 | 1,510 | | Petition to institute a public use proceeding | |
| 1452 | 110 | 2452 | 55 | | Petition to revive unavoidably abandoned application | |
| 1453 | 1,330 | 2453 | 665 | | Petition to revive unintentionally abandoned application | |
| 1501 | 1,330 | 2501 | 665 | | Utility issue fee (or reissue) | |
| 1502 | 480 | 2502 | 240 | | Design issue fee | |
| 1503 | 640 | 2503 | 320 | | Plant issue fee | |
| 1460 | 130 | 1460 | 130 | | Petitions to the Commissioner | |
| 123 | 50 | 123 | 50 | | Petitions related to provisional applications | |
| 1806 | 180 | 1806 | 180 | | Submission of Information Disclosure Stmt | |
| 8021 | 40 | 8021 | 40 | | Recording each patent assignment per property (times number of properties) | 40.00 |
| 1809 | 770 | 2809 | 385 | | For filing a submission after final rejection (see 37 CFR 1.129(a)) | |
| 2810 | 770 | 1810 | 385 | | For each additional invention to be examined (see 37 CFR 1.129(a)) | |
| Other fee (specify) _____ | | | | | | |
| Other fee (specify) _____ | | | | | | |

SUBTOTAL (3) \$ 40.00

*Reduced by Basic Filing Fee Paid

SUBMITTED BY:

Typed or Printed Name: Richard Aron Osman

Signature  Date November 13, 2003

Reg. Number 36,627 Deposit Account User ID _____
(complete if applicable)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ames et al.

Serial No. Not yet assigned

Filed: Herewith

For: *Primary N-hydroxylamines*

Group Art Unit: Not yet assigned

Examiner: Not yet assigned

Attorney Docket No. B00-001-3

Date: November 13, 2003

This application is a continuation of US Serial No 10/038,135, filed 10/20/01, which is a continuation of US Serial No 09/429,412, filed 10/28/99, now US Pat No 6,455,589.

TRANSMITTAL LETTER

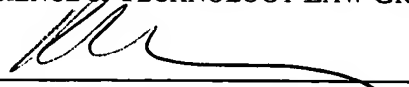
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This application is a continuation of Serial No. 10/038,135, filed October 20, 2001 which is a continuation of Serial No. 09/429,412 filed October 28, 1999, now US Pat No. 6,455,589, both having the same title and inventors. The enclosed Specification is identical to that of prior application 10/038,135, except for minor formatting changes, a cross-reference to the parent applications, incorporation of a definition of prodrug from Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pa. (the copyright and excerpted page 1654 are attached) which was expressly incorporated by reference in the parent application, and a new set of claims. As noted in the Specification, a corresponding nitrone means a nitrone condensate of the hydroxylamine and hence, having the same nitrogen bound R group, i.e. the condensation product of the primary N-hydroxyl amine with an aldehyde. These changes introduce no new matter.

The new claims are identical to claims issued in US Pat No. 6,455,589, except that the recitations of the redundant "R", "solid", and "substantially free ..." are canceled, and the recitation of a corresponding nitrone prodrug is added.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP


Richard Aron Osman, J.D., Ph.D., Reg. No. 36,627
75 Denise Drive, Hillsborough, CA 94010
Tel: (650) 343-4341; Fax: (650) 343-4342

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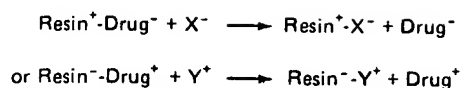
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where X^- and Y^+ are ions in the GI tract.

Fig 92-10.

exchange cationic drugs such as those with an amine functionality. Examples of some of these drugs are amphetamine, phenyl *t*-butylamine (phentermine), phenyltoloxamine, and hydrocodone, as shown in Table VI.

Prodrugs

A prodrug is a compound formed by chemical modification of a biologically active compound which will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects, such as GI irritation by aspirin. On this basis, one does not generally classify a prodrug as a sustained-release dosage form. However, the ability to bioreversibly modify the physicochemical properties of a drug allows better intestinal transport properties and hence influences the drug blood level versus time profile. Thus, prodrugs can be used to in-

Table VI—Ion Exchange Products

| Product | Active ingredient(s) | Manufacturer |
|--|-----------------------------------|--------------|
| Biphetamine capsules | amphetamine, dextroamphetamine | Pennwalt |
| Tussionex capsules, tablets, suspension | hydrocodone, phenyltoloxamine | Pennwalt |
| Ionamin capsules | phentermine | Pennwalt |

crease the strategies for sustained release and, in a limited sense, can be sustaining in their own right.

As an example of the use of a prodrug as a sustaining mechanism, consider a water-soluble drug which is modified to a water-insoluble prodrug. The prodrug will have a slower dissolution rate in aqueous fluid than the parent drug and thus the appearance of the parent drug in plasma will be slowed. This is observed with theophylline and its prodrug 7,7'-succinyliditheophylline. Alternatively, a water-soluble prodrug of a water-insoluble parent drug can be made to be a substrate for enzymes in the brush border region of the microvilli. The water-soluble prodrug complexes with the enzyme just prior to reaching the membrane surface, is metabolized, and its membrane/water partition coefficient increases. The result is an increase in the blood level of the drug. See Chapter 27.

Parenteral Dosage Forms

The most common types of dosage forms used for parenteral sustained-release drug therapy are intramuscular (IM) injections, implants for subcutaneous tissues and various body cavities, and transdermal devices. Due to physiological and anatomical constraints, many of the other parenteral routes of administration, eg, intravenous, intraarterial, intrathecal, and intraperitoneal, are not as useful in this regard. The application of the former three types of dosage forms to sustained-release drug delivery will be discussed in this section. The final section is devoted to other parenteral dosage forms being developed for targeted drug delivery.

Intramuscular Injections

Complex Formation

The formation of a dissociable complex of a drug with a macromolecule is the same physicochemical phenomenon which occurs when a drug binds to a plasma protein. In this sense, the drug-macromolecule complex can serve as a reservoir at the site of injection for sustained drug release to the surrounding tissues. The macromolecules used are either biological polymers such as antibodies and proteins, or synthetic polymers such as polyvinylpyrrolidone or polyethylene glycol. Drug release from the polymer is governed by the degree of association, as given by the following equation,

$$D + P \xrightleftharpoons{K_a} DP \quad (33)$$

where D , P , and DP represent drug, polymer, and complex, respectively, and K_a is the apparent association constant. Only that fraction of the drug which is free, f , can be absorbed;

$$f = \frac{(D)}{(DP) + (D)} = \frac{1}{1 + K_a(P)} \quad (34)$$

where (D) , (P) , and (DP) are equilibrium concentrations of drug, polymer, and complex, respectively. If $K_a(P)$ is much greater than 1, Eq 34 reduces to,

$$f = 1/[K_a(P)] \quad (35)$$

The rate of absorption of the drug, $d(C)/dt$, is therefore described by,

$$d(C)/dt = k_a f (D_t) = [k_a (D_t)]/[K_a(P)] \quad (36)$$

where (D_t) is the total drug concentration at the absorption site, ie, $(DP) + (D)$, and k_a is the absorption rate constant. It can be seen from Eq 36 that the rate of absorption can be controlled effectively by the type and concentration of polymer used, assuming that dissociation is instantaneous compared to absorption.

Complexes can also be formed between drugs and small molecules rather than macromolecules. The motive behind formation of a drug-small molecule complex is to alter the physicochemical properties of the drug and thus affect changes in its biological disposition. Unlike macromolecular complexes, drug-small molecule complexes are capable of being absorbed. They usually have very small association constants, however, which means that most of the drug is free. This nullifies any advantage gained from alteration of properties upon complexation. If the drug molecule is large relative to the complexing agent, the association constant will be greater and the complex more stable. This is the approach that has been taken commercially with polypeptide hormones, such as adrenocorticotrophic hormone (ACTH) and insulin, and with vitamins such as cyanocobalamin (vitamin B₁₂). The ACTH product, Acthar Gel HP (*Armour*) consists of an ACTH-zinc tannate complex suspended in a gelatin solution. Tannic acid acts as the complexing agent and gelatin inhibits protein binding of ACTH. An analogous product is Depinar (*Armour*), which is a cyanocobalamin-zinc tannate complex suspended in sesame oil. With both of these products, the sustained effect is due to, among other things, a reduction in solubility of the parent drug upon complexation, and not dissociation. In this respect they are much like aqueous suspensions.

Aqueous Suspensions

The rate-limiting step in drug release from an aqueous suspension is dissolution, as given by the Noyes-Whitney equation (Eq 28). The parameters influencing dissolution